07/715,272 06/11/91

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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

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EXAMINER

ART UNIT	PAPER NUMBER
	13

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 7/13/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. 3 pages
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-16 are pending in the application.
   Of the above, claims 14-16 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-13 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

Applicant's election of Group 1, in Paper No. 12, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse. See M.P.E.P. 818.03(a).

Claims 1-10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject, matter which applicant regards as the invention. Claims 1, 3, 4, 5 and 7 are indefinite in the use of the language "import antibody" in that it is not clear what constitutes an important antibody, ie. what the determines what is to be an import antibody. Claim 1 step a) is indefinite in that it is not clear what is meant by a "consensus human variable domain". Claim 1 step d) is indefinite in that it is not clear what is actually taking place when one aligns the amino acid sequences of the FR, ie. is this a physical or mental step? Claim 1 step e) is unclear in what type of homology is indicated, ie. are conservative amino acids considered as homologs or should their be identical amino acid residues at the indicated portion of the framework. Claim 1 step f), 3 is indefinite in the use of the language "participates" in that the nature of participation is unclear. Claim 1 step f) is indefinite in that it is not clear how one of ordinary skill can determine the effects which are listed in steps 1-3, ie. through antigen binding, through hybridization? Claim 1 step g) is indefinite in that it is not clear what effects are reasonably expected to occur. Claim 2 is indefinite in that the antecedent basis for "the domain" is unclear. Claim 3 is indefinite in that it is not clear when in the process of making the antibody one would search for the glycosylation sites. Claim 4 is indefinite for the same reason that claim 3 is indefinite. Claim 5 is indefinite in that it is believed that the claims up to this point were directed to making a

"humanized antibody", and it is unclear how "preparing a humanized antibody" in claim 5 differs from the preparation of the antibody up to this point. Furthermore, it is not clear what is intended in the preparation of the antibody of claim 5. Claim 6 is vague in that it is not clear what the numbers are meant to designate. It is suggested that applicant clarify the nature of the numbers or point to a figure. Claim 7 is indefinite in that it is not clear what the method is drawn to. it is suggested that the language "a method of making a humanized antibody" be inserted within the claim.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately describe the invention and failing to adequately teach how to make and or use the invention, ie. failing to provide an enabling disclosure. The following terms lack enablement in the specification:.

Claims 1 and 7 lack enablement in the language "at least a portion of an import variable domain". Applicant has only indicated specific residues which may be transferred, but they are claiming an antibody wherein the a portion of the import antibody are to be transferred. There is no guidance in the specification which would enable one of skill in the art to make antibodies with

transferred variable domains other than CDRs. Applicant is aware that a portion of the variable domain can be any one of the CDRs as well as the framework regions. However, this language also reads on small amino acid sequences which are incomplete regions of the variable region of the antibody. There is no support in the specification for linking the variable region of the antibody to any or all of the myriad "portions" which are encompassed within this language. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed. It is suggested that the specific portion of the human variable region which is described in the specification be recited within the claim or this language be removed completely in order to obviate this rejection.

Claim 1 step c) lacks enablement in that it is not clear how one would determine which amino acids are to be substituted. There is no specific recitation of what characteristics of the amino acids are necessary for deciding whether it is to be replaced or not. Without this description one of skill in the art would not be able to choose the appropriate amino acid residues without hindering the function of the antibody.

Claim 1 step f), lacks enablement in that the protocol for determining whether the amino acid residues in the import amino acid sequence are reasonably expected to interact with the antigen is not described anywhere in the specification. There is no

explicit step which enables one of ordinary skill in the art to determine the effects which are recited. It would require undue experimentation of one of ordinary skill in the art to make the variations which may be made in order to test the effects of the mutant antibodies.

Claim 2 lacks enablement in that there is no description in the specification of how to determine which residues are exposed on the surface or which residues are buried within the domain, is this through computer modeling or through x-ray crystallography or other methods?

Claim 3 lacks enablement in that there is no guidance in the specification on how one would determine which glycosylation site affects antigen binding, or what comprises "reasonable expectation".

Claims 6, 7 and 9 lack enablement in that it would appear that these amino acids are relevant to IgG and not to other isotypes. There is no indication that one of skill in the art would extrapolate the use of these amino acids to all or other isotypes of immunoglobulins. Furthermore, there is insufficient description and guidance in the specification with regards to the properties of these amino acids which would enable one of ordinary skill in the art to make humanized antibodies with other isotypes using these amino acid sequences.

Applicant has not shown that antibodies which have been modified as that which is claimed are capable of functioning as that which is being disclosed, ie. maintaining the binding affinity of the parent antibody. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Burgess et. al. Journal of Cell biology, 111: 2129-2138 (1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Lazar et. al. Molecular and Cellular Biology, 8:1247-1252 (1988). Similarly it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies. See Tao et. al. The Journal of Immunology, Vol. 143, No. 8. 2595-2601 (1989) and Gillies et. al. Human Antibodies and Hybridomas, Vol 1, no. 1, 47-54 (1990). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity and characteristic of a protein. Therefore, without sufficient guidance in the

specification to support the use of the above terms and for the reasons mentioned above one of ordinary skill in the art would forced into undue experimentation in order to practice the invention as is claimed.

Claims 1-11 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

35 U.S.C. § 101 reads as follows:

> **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.**

Claims 1-4, 6-8 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The above claims are drawn to a method of preparing an antibody, however, there is no indication within the claims that actual physical steps are taking place. For example, there is no step which includes isolating an antibody, rather obtaining an amino acid sequence. All of the steps which are listed in the claims can be done on paper as mental steps or on a computer terminal.

The specification is objected to under 35 U.S.C. § 112, first paragraph, and claims 9-13 are rejected under 35 U.S.C. § 112, first paragraph and 35 U.S.C. § 101 as the specification fails to adequately teach how to use the claimed monoclonal antibodies in the manner in which they are disclosed ie. for the therapeutic

purposes. Applicants claims are supported only by in vitro data showing the ability of muMab4D5, which is a humanized anti-p185 antibody which reacts with breast and ovarian cancers, to react with different cell lines (see page 88-90 of the specification). Applicant has made no showing that these data correlate with utility for in vivo therapy in humans of the complex array of diseases encompassed by the claims. In general, effective treatment of human cancers has not been routinely achieved in the art using monoclonal antibodies. Further, in vitro data such as that reported in the specification and animal model studies frequently do not correlate with clinical utility in in vivo trials in patients. Based on the evidence of record, the alleged utility of the claimed composition for the treatment of cancer would not be believable on its face to the person of skill in the art in view of the contemporary knowledge in the art. Applicant has not provided any showing of therapeutic utility of the subject monoclonal antibodies which would lead one of skill in the art to believe that the antibodies are broadly applicable for the treatment of all types of autoimmune diseases. Applicant is required to provide evidence commensurate with the scope of the claims, which would be convincing to those skilled in the art that the claimed compositions have utility for the treatment of malignant and autoimmune diseases in humans. See MPEP 608.01(p).

Waldmann, in a recent review of the literature pertaining to clinical applications of monoclonal antibodies for diagnosis and therapy of human disease, teaches that effective therapy using monoclonal antibodies has been elusive and indicates that hopes for antibody-based treatment methods engendered by in vitro studies have not correlated well with in vivo clinical trial results in patients with cancer. It does not appear that the exemplary material provided in the specification in support of the assertions that the claimed antibodies have therapeutic utility would be viewed by those skilled in the art as being predictive of their utility for treating humans. Applicant has not exemplified how to use the claimed antibodies in vivo and has not shown that the antibodies would be effective in vivo. It appears that undue experimentation would be required of one skilled in the art to practice the claimed invention for the single utility disclosed in the specification.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless--

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this country or a

> **foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> **A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**
>
> **Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.**

Claims 1, 2, 5-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Queen et. al.. The above claims are drawn to a method of producing a humanized antibody wherein the amino acid sequences of an import antibody and a consensus antibody are compared, wherein the CDRs of the import antibody are substituted for the antibody of the consensus antibody, and wherein certain framework residues which are responsible for the binding of antigen, interaction with CDR, or participating in the Vl-Vh interaction are also imported to the consensus antibody. In essence, residues of the framework region are also transferred with

the CDRs in order to retain the antigen binding affinity of the parent antibody.

Queen et. al. describe the production of humanized antibodies wherein the murine antibody is compared to human antibodies and the most homologous human antibody is chosen as the acceptor molecule. The CDRs of the murine antibody are then substituted for the CDRs of the human antibody and certain framework residues are also changed. Queen et. al. describe computer modeling and sequence comparison in order to determine the amino acid residues which are to be substituted (see page 10031-10033). Although the steps of the methods are not in exactly the same order, all of the claimed elements are present with in the reference.

Claims 1,2 and 5-10 are rejected under 35 U.S.C. § 102(a) as being anticipated by Co et. al.. See above discussion.

Co et. al. show the production of humanized anti-HSV using the general concept of Queen et. al. (see Results and Table 1).

Claims 3 and 4 are rejected under 35 U.S.C. § 103 as being unpatentable over Queen et. al. or Co et. al. in view of Wallick et. al.

The above claims are drawn to a method of making a humanized antibody wherein the CDRs of an import antibody are transferred to a consensus human antibody along with certain residues of the framework. Furthermore, the claims require that the glycosylation

sites, if any, of the import amino acid also be imported with the CDRs and framework regions if these sites have an affect on the binding of antigen.

Queen et. al. and Co et. al. both describe the production of humanized antibodies by transferring the CDRs and certain framework regions of the donor antibody to the human consensus antibody (see Queen et. al. pages 10031-10033 and Co et. al. page 2871). They further state that any residue which might have an affect on the antigen binding of the antibody should be changed substituted in order to maintain the binding affinity of the parent antibody (see page 10033 of Queen et. al. at the last paragraph on the page). They do not however, specifically discuss the glycosylation sites as potential targets for transfer. Wallick et. al. teach the importance of carbohydrate interaction with antigen for maintaining or increasing antigen binding affinity (see pages 1107-1108). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make humanized antibodies using the method of Queen et. al. or Co et. al. and further incorporating the concept taught by Wallick et. al.. One of ordinary skill in the art would have been motivated to combine the teachings of the two references in view of the teaching of Queen that retaining high antigen binding affinity is desirable in the production of humanized antibodies. Knowing the role of carbohydrates in antigen antibody interaction as was pointed out by

Wallick et. al. one of ordinary skill would have had the means and the motivation to make humanized antibodies using both of the teachings of the primary and secondary references.

Claim 11 is rejected under 35 U.S.C. § 103 as being unpatentable over Queen et. al. or Co et. al. in view of Reichmann et. al.

The above claim is drawn to a humanized antibody wherein only one amino acid (listed in claim 9) in the framework and the CDRs have been substituted in the consensus antibody.

Queen et. al. and Co et. al. both teach the production of humanized antibodies by transferring the CDRs of a murine antibody along with specific residues of the framework region to the acceptor antibody molecule. They do not however teach only substituting one of the framework residues among those listed in claim 9. Queen et. al. introduce the general concept of a scaffold wherein certain amino acid residues of the framework must be present and certain are dispensable. Reichmann et. al. teach that a single amino acid substitution in an antibody is sufficient to retain the antigen binding specificity of the parent antibody (see final paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make only a single substitution in the antibody of Queen et. al. or Co et. al. in positions among those listed in claim 9. It would have been obvious to one of ordinary skill to complete the

invention in light of the success of Reichmann et. al. in only mutating one amino acid of the framework. Knowing that each antibody varies slightly in the non-conserved region, and given the computer modelling protocol set forth by Queen et. al. one of ordinary skill would have been motivated to make a single mutation in the variable region with the expectation of obtaining a functional antibody.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lila Feisee whose telephone number is (703) 308-2731.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Feisee/lf
September 29, 1992

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
9/30/92